Modelling the 2001 Foot-and-Mouth Epidemic in Uruguay using Geo-referenced Data

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June 6, 2005

Abstract

Foot-and-mouth disease (FMD) is a highly infectious illness of livestock and a serious economic threat. We modelled the 2001 FMD epidemic in Uruguay using an explicit discrete spatial epidemic model (comprising a series of coupled differential equations) that includes geo-referenced data (i.e., Euclidean distances between farms, as estimated in relation to distances between county centroids). The value of spatially explicit models in the development and testing of FMD control measures was tested using the corresponding spatially homogeneous model as basis for comparison. We estimated model parameters using least-squares fitting techniques and assessed parameter uncertainty using the stochastic temporal dependence of the cumulative number of outbreaks. The limitations of spatially homogeneous models were illustrated by their inability to capture observed patterns of spread effectively. For the situation of Uruguay, our discrete spatial model captured a double peak in the epidemic, a pattern not observed under the spatially homogeneous model. We defined internal (within counties) and external (across counties) reproductive numbers, that is, within-and across-county contributions to the average number of secondary infections. Following movement restrictions, the mean internal $\bar{R}^{in} \approx 87$, while the external $\bar{R}^{out} \approx 0.82$. Twelve days after the start of the mass vaccination policy, the internal reproductive number dropped to less than one. We explored the expected impact of how quickly movement restrictions are implemented after the start of an outbreak. Our model predicts that, if the movement restrictions had been delayed an additional three days, there would have been 26% more outbreaks. If the movement restrictions had been implemented 3 days prior to the actual date, our model predicts the epidemic would have

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†Los Alamos Unclassified Report LA-UR-04-5400

been reduced by 23%.

Keywords: Foot-and-mouth Disease; spatial mathematical model; reproductive number; Uruguay; movement restrictions; mass vaccination.

1 Introduction

Foot-and-mouth disease (FMD) is a highly infectious illness caused by an aphthovirus that affects cloven-hoofed animals such as pigs, cattle, and sheep. Infected animals shed large amounts of the virus through the mouth and nose (Sutmoller et al., 2003). The virus can survive in objects such as shoes, clothes, or vehicle tires. The wind can carry the virus long distances (Gloster et al., 2003; Sutmoller et al., 2003). Recurrent FMD outbreaks have occurred in several regions of the world. In South America, FMD was first recorded in Argentina, Uruguay, and Brazil around 1870 as a result of the introduction of cattle from Europe during the early colonization days (Saraiva, 2004). South America has reported recurring outbreaks of FMD, albeit the number of clinical FMD cases in that region has decreased considerably since the signing of the Hemispheric Plan for the Eradication of Foot-and-Mouth Disease (PHEFA) in 1987 (Correa Melo et al., 2002).

The likelihood that FMD will start an epidemic outbreak depends on various factors that include the susceptibility of the livestock, the potential modes of transmission, and the effectiveness of public health control and intervention efforts. Control and intervention efforts have been based, since 1911, on the concept of the basic reproductive number introduced precisely for these purposes by Sir Ronald Ross (Ross 1911) and his "pupils" Kermack and Mckendrick

(Kermack and Mckendrick, 1927). The basic reproductive number, R_0, is defined as the number of secondary cases generated by a primary case when the virus is introduced in a population of fully susceptible individuals at a demographic steady state (Diekmann and Heesterbeek, 2000). That is, R_0 measures the power of a disease to invade a population under conditions that facilitate maximal growth. Once an outbreak starts, the number of susceptible livestock decreases either through loss of susceptibles (i.e., they get infected) or from the implementation of control measures such as slaughter or vaccination that effectively reduce the force of infection. The number of secondary infections once the initial epidemic phase has begun becomes a dynamic process. That is, after the initial phase, it tends to decrease. Here, we will denote the effective reproductive number at time t as $R(t)$ and assume that $R(0) = R_0$. There is no "clean" way of characterizing $R(t)$ and this theoretical issue is not resolved here. However, we make use of this concept as it illuminates the discussion since the objective of disease contingency plans are to make $R(t) < 1$. The timeliness and effectiveness of the response effort is critical in the case of FMD (Rivas et al., 2003a).

The transmission dynamics of FMD involve immunological, epidemiological, geographical, and sociological factors. The detailed role of some immunological and epidemiological factors has been relatively well studied. For example, it has been recently shown experimentally (in pigs and cattle) that the rate of spread, the incubation period, and disease severity depend on the dose received, the route of introduction, the animal species, and husbandry conditions (Alexandersen et al., 2003). The average incubation period for FMD has been reported to be 3-6 days with a maximum of 14 days (Hugh-Jones and Wright, 1970; Hugh-Jones and Tinline,

1976; Sellers and Forman, 1973). A recent experimental study in cattle reports the presence of viral RNA (mouth and nasal swabs) in all infected cattle within 24 h post infection with peak levels 1-2.5 days after infection. In some animals viral RNA was not detected until 7-18 days post infection (Zhang et al., 2004). Latent animals progress to an infectious state that lasts for about 8 days. They are typically asymptomatic during the first 5 days of the infectious period (Keeling et al., 2001) and then asymptomatic and infectious (Zhang et al., 2004). Hence, there is a small window (3-5 days) to detect and remove or isolate the infected animals from the rest. Animals that recover do so but with reduced weight and a diminished productivity (Ferguson et al., 2001) .

The transmission dynamics of FMD is tied in to geographical and sociological factors that are difficult to separate and/or quantify. FMD transmission between adjacent farms has been documented (Keeling et al., 2001; Ferguson et al., 2001; Kao, 2002). Long distance transmission through routes that include daily milk collection routes, cattle transportation, animal movement, or cattle rellocation, etc. are not only possible but extremely likely (Sellers et al., 1971; Anon, 1969). No models that include explicit transmission mechanisms (cause and effect), that is, deterministic models, have been able to incorporate all possible transmission routes effectively. There have been some valiant efforts for the case of human influenza (Elveback et al., 1964) and recently for FMD (Bates et al. 2003). The agent-based model known as EpiSims (Eubank et al. 2004) provides an example of the cost and magnitude of validating a detailed model. Cerrtainly, we have gained some understanding from the outcomes of semi-deterministic models like EpiSims (Eubank et al. 2003) but challenges remain (Chowell et al. 2003). Simple

deterministic models can often yield useful insights, generate intriguing hypotheses, and guide future research (Anderson and May, 1991) and their analyses can be used quite roughly to evaluate the validity of control and intervention measures. Models that incorporate the immunological, epidemiological, sociological, and geographical dependent factors just described in the context of FMD would be extremely complex. Their validation would require knowledge of a large number of parameters, their distributions, and large amounts of data. The information required would include knowledge of the rates of movements of key individuals, human and animal traffic between farms, lags in reporting, impact of holidays, highly heterogeneous contact structures (between susceptible hosts, "vectors", and infected hosts), geography as well as immunological (variability in susceptibility) and epidemiological factors (variable latent and incubation period distributions) factors. Prior work (Rivas et al. 2003a; 2003b) provides rough quantitative estimates of the importance of geographical factors on the rate of FMD spread. It was shown that intervention response times of farms depended strongly on the spatial (regions) distribution of farms, a dependence used to develop a data-base simulation of the 2001 FMD epidemic in Uruguay (supplementary materials).

1.1 FMD Britain versus Uruguay

The cost of FMD epidemics can be high. More than four million animals were destroyed during the 2001 FMD epidemic in Great Britain (Enserink, 2001) and the exportation of animal goods cancelled for roughly a year. During the 2001 FMD epidemic in Great Britain, two teams of researchers developed highly refined models to aid in the decision-making process (Keeling et

al., 2001; Ferguson et al., 2001) and concluded that massive culling was the best strategy to control the ongoing FMD epidemic. Their conclusions relied on models that incorporated data on the location of farms, farm animal density, and measures of animal heterogeneity within farms. Longitudinal data on the number of farms infected and the culling process were available (Enserink, 2001).

The first outbreak of the 2001 FMD epidemic in Uruguay was reported in the state of Soriano, close to the border with Argentina, on April 23 (Irvine, 2004; reports of the European Commission). The epidemic spread through regions where it had not previously existed (exotic disease) and geo-referenced data was collected. In just a few days, FMD spread throughout the entire country. The epidemic reached its peak incidence (66 new outbreaks) on May 25, with a total of 1762 reported infected farms by July 10, 2001 (Figure 1). Animal slaughter took place from April 25 to April 29 (total: 5,295 cattle, 1.481 sheep, 332 pigs) while animal movement restrictions were enforced by the police and the army as of April 27, four days after the first reported outbreak. People movement was never banned (farm personnel continued to come in and out during the roadblock period). An awareness campaign to farmers through press releases and personal visits by veterinarians to farms was implemented. Export controls were implemented at borders, airports, and harbors (reports of the European Commission). Mass vaccination (60-70% expected efficacy) started on May 5 with May 28 as the expected completion date. No high potency vaccines (where protective immunity is reached within 3-4 days (Doel, 2003)) were used. Hence, peak protective levels of the serum antibodies from vaccination were expected to take 14-28 days. The vaccination programme did not include calves

younger than 3 months, pigs, or goats. Vaccines were delivered to county/district veterinarians who provided them to farmers who administered them to their farm herds. The second round of mass vaccination (booster vaccination with expected 100% efficacy) started on June 15 and was completed on July 22. The estimated cost of controlling the epidemic was 13.6 million US$ of which 7.5 million were spent on vaccine purchase (Sutmoller et al., 2003).

1.2 Modelling approach

We modelled the epidemic using a discrete spatial deterministic epidemic model that includes geo-referenced data (i.e., euclidean distances between farms, as estimated in relation to distances between county centroids). We assessed the ability of this spatially explicit model, where space serves as a proxy for factors that have not been measured, to capture the transmission dynamic patterns of the FMD epidemic in Uruguay. Epidemiological and control parameters are estimated using least-squares fitting. Internal (within counties) and external (across counties) reproductive numbers before and after interventions were implemented, are computed. The impact of time delays on the implementation of movement restrictions was explored (Castillo-Chavez et al., 2003). A spatially homogeneous model is also used to contrast the limitations of their qualitative predictions in the context of FMD in Uruguay.

2 Modelling framework

An explicit discrete spatial deterministic model that incorporates specific interventions is introduced. The number of secondary outbreaks generated by a primary outbreak during its entire period of infectiousness are classified as *internal* (within counties) and *external* (across counties). Interventions in the 2001 FMD epidemic were implemented after the initial outbreak. Hence, control parameters are modelled as simple functions of time. Parameter values are estimated from data using least-squares fitting techniques. Standard deviations for the estimated parameters are also provided.

2.1 Spatial epidemic model

The epidemiological unit is the farm. Farms are classified as susceptible (S), latent (L), infectious and undetected (I), and detected and removed (J). Farms are aggregated at the level of counties (Table 1). A susceptible farm in county i that is in contact with the virus enters the latent (uninfectious and asymptomatic) class (L) at the rate $\sum_{j=1}^{n} \beta_{ij} I_j$. In other words, the rate of infection is assumed to be proportional to the sum of the weighted prevalences of infected farms from all counties j. Hence, the transmission parameters β_{ij} measure the impact on county i from direct and indirect "contacts" between $i-$county and the $j-$county. These "contacts" may be the result of animal rellocation or movement, from the sharing of milk routes (drivers as "mechanical" vectors or carriers), shared veterinarians or overlapping visitors (buyers, salesmen of farm products, etc. Sutmoller et al., 2003; Sellers et al., 1971). Far away farms are assumed to be less likely to share the same veterinarians or milk trucks or visitors. Having no reliable

information on the county specific frequency of movement of potential "carriers." It is assumed that the rate of transmission β_{ij} between farms in counties i and j decays exponentially fast with the Euclidean distance of their respective county centroids. The elements of the "mixing" or "contact" matrix β_{ij} (Anderson and May, 1991) are therefore expressed as:

$$\beta_{ij} = \beta(t)\ e^{-qd_{i,j}}, \tag{1}$$

where $\beta(t)$ denotes the average transmission rate of infectious farms within each county at time t, d_{ij} is the distance between the centroids of counties i and j (Figure 2); and the parameter q (1/km) which quantifies the extent of average local spread ($1/q$ can also be interpreted as the FMD mean transmission range). Small values of q lead to widespread influence, whereas large values of q support the hypothesis that local spread is the key. For simplicity, uniform mixing within each county is assumed, that is, $d_{ii} = 0$. It is also assumed that latently infected farms "progress" towards the infectious class after a mean time of $1/k$ days and that infectious farms are detected and isolated from other farms at the per-capita rate α. That is, α is the average time required to detect and isolate an infected farm.

The above definitions and assumptions lead to the following FMD model:

$$\begin{cases} \dot{S}_i &= -S_i \sum_{j=1}^{n} \beta_{ij} I_j \\ \dot{L}_i &= S_i \sum_{j=1}^{n} \beta_{ij} I_j - kL_i \\ \dot{I}_i &= kL_i - \alpha I_i \\ \dot{J}_i &= \alpha I_i. \end{cases} \tag{2}$$

The dot denotes time derivatives while S_i, L_i, I_i, and J_i denote the number of susceptible, latent, infectious, and removed/isolated farms in county i ($i = 1, 2, ..., n$). The distribution of the number of farms per county is given in Table 1. The above system falls within the class of metapopulation models that have been used extensively to study ecological processes in heterogeneous patchy environments. In fact, the spatially dependent transmission rates $\{\beta_{ij}\}$ correspond to the metapopulation patch connectivity index (Hanski, 1998) once we re-interpret d_{ij} as a measure of the influence of the landscape on migration (Moilane and Hanski, 1998). The elements of $\{d_{ij}\}$ here are set of as "indices" that capture the effects of local transmission factors such as wind direction and animal heterogeneity within farms (dairy, beef, etc.). Here, the county connectivity d_{ij} is approximated by the distance between counties. The incorporation of a few time-dependent control/interventions measures leads to the following modified model (see compartment diagram in Figure 3) :

$$\begin{cases} \dot{S}_i &= -S_i(t)\sum_{j=1}^{n}\beta_{ij}(t)I_j(t) - \nu(t)S_i(t) \\ \dot{V}_i &= \nu(t)S_i(t) - V_i(t)\sum_{j=1}^{n}\beta_{ij}(t)I_j(t) - \mu(t)V_i(t) \\ \dot{L}_i &= (S_i(t) + V_i(t))\sum_{j=1}^{n}\beta_{ij}(t)I_j(t) - k(t)L_i(t) \\ \dot{I}_i &= k(t)L_i(t) - \alpha(t)I_i(t) \\ \dot{J}_i &= \alpha(t)I_i(t) \\ \dot{P}_i &= \mu(t)V_i(t) \end{cases} \tag{3}$$

where the classes S_i, L_i, I_i and J_i are defined as before. Susceptible farms in county i (S_i) are vaccinated at rate ν (V_i); vaccinated farms in V_i enter the protected class P_i at rate μ; vaccinated farms in county i that have not yet reached protective levels (class P) enter the latent (uninfectious and asymptomatic) class (L) at the rate $\sum_{j=1}^{n}\beta_{ij}I_j$. The total cumulative number of reported infected farms as a function of time is given by $C(t) = \sum_{i=1}^{n} J_i(t)$ while the

daily number of new reported infected farms is given by $\dot{C(t)}$, that is by $\alpha(t)\sum_{i=1}^{n} I_i(t)$.

The dependence of parameters $\beta(t)$, $\alpha(t)$, $\nu(t)$, and $\mu(t)$ on time allow for the possibility of implementing control measures at different times (Chowell et al., 2004). For simplicity, these parameters are modelled as simple step functions

$$\beta(t) = \begin{cases} \beta_0 & t < \tau_m \\ \beta & t \geq \tau_m \end{cases} \tag{4}$$

$$\alpha(t) = \begin{cases} \alpha_0 & t < \tau_v \\ \alpha & t \geq \tau_v \end{cases} \tag{5}$$

$$\nu(t) = \begin{cases} 0 & t < \tau_v \\ \nu & t \geq \tau_v \end{cases} \tag{6}$$

$$\mu(t) = \begin{cases} 0 & t < \tau_v \\ \mu & t \geq \tau_v \end{cases} \tag{7}$$

where $\tau_m = 5$ (27 April 2001) is the time when movement restrictions were put in place and $\tau_v = 13$ (05 May 2001) is the time when mass vaccination was started.

2.1.1 The reproductive number

Government movement restrictions (the first intervention implemented) were put in place relatively quickly. Hence, there was not sufficient data to estimate the basic reproductive number

(R_0). We defined the *internal* reproductive number of county i, R_i^{in}, as the number of secondary outbreaks generated by an outbreak in county i within the same county after $t > 4$, $R_i^{in} = \beta N_i/\alpha$ where N_i denotes the number of farms in county i and $1/\alpha$ is the average time it takes to identify infected farms. The *external* (across counties) reproductive number of county i, R_i^{out}, is defined as the number of secondary outbreaks generated by an outbreak in county i in other counties, where $j = 1, 2, ..., n; j \neq i$. $R_i^{out} = \sum_{j \neq i}^{n} \beta N_j \; e^{-qd_{ij}}/\alpha$, that is, it is given by the additive contributions of the number of secondary cases (after the first intervention) in county i. Hence, the contributions must be weighted by distance.

Mass vaccination defined the second type of interventions. An expression for a time-dependent reproductive number that considers the impact of mass vaccination (loss of susceptibles) is defined as a function of the effective time T elapsed from the start of mass vaccination (time t_v) to the current time t. That is, if $T = t - t_v - 1/\mu$, where $1/\mu$ denotes the mean time required for a vaccinated farm to reach protective antibody levels. The *internal* and *external* post-vaccination time-dependent reproductive numbers are modelled as $R(T)_i^{in} = (\beta N_i/\alpha) \; s_i^*$ and $R(T)_i^{out} = (\sum_{j \neq i}^{n} \beta N_j \; e^{-qd_{ij}} \; s_j^*/\alpha)$ (i =1, 2, ..., n) with

$$s_i^* = \begin{cases} 0 & N_i \leq T\nu \\ 1 - T\nu/N_i & N_i > T\nu \end{cases} \tag{8}$$

Here, we have modelled or defined various reproductive numbers motivated by the "standard" versions (Anderson and May, 1991; Brauer and Castillo-Chavez, 2000). Here, they are seen as reasonable "heuristic" versions that incorporate in sensible ways available information. As noted before, a theory that characterizes a time-dependent reproductive number is still

lacking.

2.2 Spatially homogeneous case

In order to assess the role of spatial heterogeneity, a description of the corresponding spatially homogeneous version (null-model) follows. We set the homogeneous mixing assumption, $\beta_{ij} = \hat{\beta(t)}$ where

$$\hat{\beta(t)} = \begin{cases} \hat{\beta}_0 & t < \tau_m \\ \hat{\beta} & t \geq \tau_m \end{cases} \tag{9}$$

The corresponding system of nonlinear ordinary differential equations for the spatially homogeneous model becomes

$$\begin{cases} \dot{S}(t) &= -\hat{\beta(t)}S(t)I(t)/N - \hat{\nu}S \\ \dot{V}(t) &= \hat{\nu}S - \hat{\beta(t)}V(t)I(t)/N - \hat{\mu}V \\ \dot{L}(t) &= \hat{\beta(t)}(S(t) + V(t))I(t)/N - \hat{k}L(t) \\ \dot{I}(t) &= \hat{k}L(t) - \hat{\alpha}I(t) \\ \dot{J}(t) &= \hat{\alpha}I(t) \\ \dot{P}(t) &= \hat{\mu}V(t) \end{cases} \tag{10}$$

where S, V, L, I, J, and P denote the total number of susceptible, vaccinated, latent, infectious, removed/isolated, and protected farms, respectively. The parameters $\hat{\alpha(t)}$, $\hat{\nu(t)}$, and $\hat{\mu(t)}$ depend on time in the same manner as in the spatially explicit model.

3 Model implementation

The epidemic-curve data on the number of outbreaks reported over time identified by counties were obtained from geo-referenced outbreak reports. Intercounty distances (i.e., Euclidean distances between farms, as estimated in relation to distances between county centroids) were used as a measure of the connectivity between counties. Epidemiological and control parameters were estimated from the cumulative number of infected farms by a least-squares fit.

The 19 Uruguayan states are grouped into three contiguous regions (Regions I, II and III) (Figure 4b). They experienced significantly different prevalences (Rivas et al. 2003a). Most cases accumulated in Region I where the epidemic started. Fewer cases occurred in the surrounding Region II, and the least number of cases were reported in Region III (Rivas et al. 2003a). Table 1 shows the distribution of the number of counties per state and the mean density of farms per county in each Uruguayan state. Figure 2 shows the distribution of all the intercounty distances. Using geo-referenced outbreak reports obtained from public records of the Uruguayan Ministry of Livestock, Agriculture, and Fisheries (MGAP), the Pan-american Health Organization, and the World Organization for Animal Health (OIE) were used to construct a table of the number of daily new reported infected farms during the first 79 days of the epidemic. That is, a table of the form (t_i,x_i), $i = 1, ..., 1762$, where t_i denotes the time and x_i the location of the i^{th} reported infected farm was constructed from the data. Hence, each infected farm was associated geographically with a region, state, and county. Table 1 shows that the focus of the epidemic was in Region I where the epidemic started (1003 outbreaks (57%)). This region includes the states of Soriano, with 463 outbreaks (26%); Colonia, with

362 (21%); and Rio Negro, with 178 (10%).

3.1 Parameter estimation

As in the demographic literature, the intrinsic growth rate was defined as the number of outbreaks per day. The initial region-specific intrinsic growth rates r_i (i =1,2,3) were estimated under the assumption of exponential growth. That is, r (with units of 1/day) was estimated by assuming that the cumulative number of reported farms was proportional to $\exp(rt)$, where t is the time (in days). Solving for r, we obtained $r = (ln(y(t)) - ln(y_0))/t$, where ln denotes natural logarithm and y_0 is the number of outbreaks reported the during the first reporting day. The intrinsic growth rate in Region III was estimated using the cumulative number of outbreaks from May 02 to May 07, 2001. This window of time was chosen because of a pattern of significant underreporting prior to May 02.

The model parameters $\mathbf{\Theta} = (\beta(t),\ k(t),\ \alpha(t),\ q(t),\ \nu(t),\ \mu(t))$ and the initial number of exposed and infectious farms ($E(0)$ and $I(0)$) were estimated from the cumulative number of reported farms (t_i, y_i), where t_i denotes the i^{th} reporting time (79 reporting days) and y_i is the cumulative number of reported farms by least-squares fitting to $C(t, \mathbf{\Theta})$ (the cumulative number of reported farms for our ODE model with interventions (3)) in Region I (where the outbreak started and the majority of outbreaks occurred). This gives a system of 5 (equations per county) * 42 (counties in Region I) = 210 differential equations. The farm density of each county is provided in Table 1. MATLAB (The MathWorks, Inc.) was used to carry out the

least-squares fitting procedure. Initial conditions were chosen within the appropriate ranges ($0 < \beta < 100$, $1/5 < k < 1/3$, $1/12 < \alpha < 1/4$, $0 < q < 10$, $0 < \nu < 10$, $0 < \mu < 10$). Parameter optimization was carried out using the Levenberg-Marquardt method with line-search (More, 1977). This method is implemented in the built-in routine `lsqcurvefit.m` in MATLAB (The MathWorks, Inc.). The cumulative number of reported farms $J(t)$ under a spatially homogeneous mixing ODE model (10) was also fitted to data using also the same procedure described above.

The asymptotic variance-covariance $\mathbf{AV}(\hat{\mathbf{\Theta}})$ of the least-squares estimate for the spatially explicit Model (3) was computed using a Brownian bridge error structure to model the stochastic temporal dependence of the cumulative number of outbreaks. The explicit formula used is

$$\mathbf{AV}(\hat{\mathbf{\Theta}}) = \sigma^{\mathbf{2}}\ \mathbf{B}(\mathbf{\Theta_0})\ \nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})^{\mathbf{T}}\ \mathbf{G}\ \nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})\ \mathbf{B}(\mathbf{\Theta_0}), \tag{11}$$

where $\mathbf{B}(\mathbf{\Theta_0}) = [\nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})^{\mathbf{T}}\ \nabla_{\mathbf{\Theta}}\mathbf{C}(\mathbf{\Theta_0})]^{-\mathbf{1}}$.

An estimate of $\mathbf{AV}(\hat{\mathbf{\Theta}})$ is

$$\hat{\sigma}^2\ \hat{\mathbf{B}}(\hat{\mathbf{\Theta}})\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})^{\mathbf{T}}\ \mathbf{G}\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})\ \hat{\mathbf{B}}(\hat{\mathbf{\Theta}}), \tag{12}$$

where $\hat{\mathbf{B}}(\hat{\mathbf{\Theta}}) = [\nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})^{\mathbf{T}}\ \nabla_{\mathbf{\Theta}}\hat{\mathbf{C}}(\hat{\mathbf{\Theta}})]^{-\mathbf{1}}$, $\hat{\sigma}^2 = \sum(y_i - C(t_i, \hat{\mathbf{\Theta}}))^2/(I_{1xn}\ \ \mathbf{G}\ \ I_{nx1})$ and $\nabla_{\Theta}\hat{\mathbf{C}}$ are numerical derivatives of $C(\hat{\mathbf{\Theta}})$. The error structure (Davidian and Giltinan, 1995) was also modelled by a Brownian bridge ($\mathbf{G}$) in order to account for the stochastic temporal dependence of the cumulative number of outbreaks. Here $\mathbf{G}$ is an n x n matrix with entries $G_{i,j} = (1/n)\ \min(i,j) - (ij)/n^2$ where n is the total number of observations. $\mathbf{G}$ captures the higher variability

in the cumulative number of outbreaks observed on the middle course of the epidemic as well as the smaller variability observed at the beginning and the end of the epidemic. Confidence intervals of 95% were computed using the asymptotic variance of our parameter estimates (diagonal elements of $\mathbf{AV}(\hat{\mathbf{\Theta}})$). The asymptotic variance-covariance $\mathbf{AV}(\hat{\mathbf{\Theta}}_{\mathbf{0}})$ for the nonspatial (homogeneous mixing) model can be similarly computed using $J(t)$ in model (10) instead of $C(t)$.

The improvement in goodness of fit provided by the spatial model compared to the non-spatial model was statistically assessed using the stepwise F test (Jacquez, 1996). In fact, if $RSS_{spatial}$ denotes the residual sum of squares from the spatial model and $RSS_{nonspatial}$ the corresponding sum of squares from the non-spatial (homogeneous mixing) model then

$$RSS_{spatial} = \sum_{i=1}^{n=79} (y_i - C(t_i, \hat{\mathbf{\Theta}}))^2 \tag{13}$$

$$RSS_{nonspatial} = \sum_{i=1}^{n=79} ((y_i - J(t_i, \hat{\mathbf{\Theta}}_{\mathbf{0}}))^2 \tag{14}$$

The F test is the ratio of the decrease in the residual sum of squares, divided by the decrease in degrees of freedom ($p_{spatial} - p_{nonspatial}$), all divided by the mean residual sum of squares obtained from the spatial model ($RSS_{spatial}/(n - p_{spatial})$). That is,

$$\frac{(RSS_{nonspatial} - RSS_{spatial})/(p_{spatial} - p_{nonspatial})}{(RSS_{spatial}/(n - p_{spatial}))} \sim F_{(p_{spatial} - p_{nonspatial}),(n - p_{spatial})} \tag{15}$$

where $p_{spatial} - p_{nonspatial} = 1$ (the spatial model has only one additional parameter (parameter q) than the nonspatial model). When the above ratio is greater than the corresponding value of the F distribution for the significance level chosen then we would conclude that the spatial

model significantly decreases the residual variance (Jacquez, 1996).

4 Results

Three epidemic regions could be differentiated based on the percentage of all cases occurring in each region ((Figure 4b). The initial intrinsic growth rate r (assuming initial exponential growth rate $y \propto e^{rt}$) was 0.65, 0.35, and 0.19 for Regions I, II, and III, respectively (Figure 4 b). These growth rates decayed as awareness of the epidemic increased and as the level of movement restrictions (the epidemic started to spread from Region I onwards) became more established. After May 07, the average rate of growth became about the same in all three regions (see Figure 4a). In order to reduce model complexity, we focused on the analysis of the incidence data from the epidemic Region I where the majority of outbreaks occurred (57% of total outbreaks).

The nonspatial epidemic Model (10) when fitted to the cumulative number of infected farms showed a systematic deviation from epidemic data during the first 20 days (Figure 5a). Model parameter estimates used are in Table 2. Fitting the cumulative number of reported farms in Region I to the spatially explicit model with interventions (3) gives better agreement to data (Figure 5b). Furthermore, parameter estimates (from best fit) are in agreement with FMD epidemiology (see Table 3). The spatial model fit is also statistically significant (F test; P-value < 0.01). A comparison between the daily incidence obtained from the nonspatial and the spatial model is given in Figure 6.

The "free course" of the epidemic included approximately the first 5 days, after which movement restrictions were rapidly enforced by the police and the army. Hence, parameter estimates of the transmission rate and the infectious period during the initial "free" growth of the epidemic were somewhat uncertain. The estimate for the transmission rate β_0 before movement restrictions was 0.33 (SD 0.13) per farm per day while we computed an estimate of $\beta = 0.10$ (SD 0.03) per farm per day after movement restrictions were put in place. The rates of identification and isolation of infected farms before and after movement restrictions were put in place are $\alpha_0 = 0.14$ (SD 0.02) and $\alpha = 0.14$ (SD 0.02), respectively. These values are consistent with each other.

As noted before, unfortunately, there is not enough data to generate useful estimates of the basic reproductive number, since movement restrictions were implemented just a few days after the first reported outbreak. However, it was possible to estimate internal and external reproductive numbers of $\bar{R}^{in} \approx 87.20$ and $\bar{R}^{out} \approx 0.82$. The model predicts that the *internal* reproductive number would rapidly (in approximately 12 days after mass vaccination) decrease to a number less than one (epidemic day 25, or May 16).

The estimate of the vaccination rate of susceptible farms ν turned out to be 0.25 (SD 0.09) per day. That is, a mean time of approximately 4 days was required before a susceptible farm was successfully vaccinated. Vaccination does not provide instantaneous protection against FMD. Our estimate for the rate at which vaccinated farms reach protective antibody levels μ is 0.14 (SD 0.03) per day. That is, 7.14 days are required on the average before successfully

vaccinated farms become protected. The estimate for q is 1.03 1/km (SD 0.10). That is, the average transmission range ($1/q$) is approximately 0.97 km.

A 3-day delay in the implementation of movement restrictions with respect to the actual implementation date yields 1262 infected farms (26% increase in the final epidemic size). If the movement restrictions had been implemented 3 days prior to the actual date, the model would then yield 775 infected farms (a 23% decrease from the actual epidemic size; Figure 7).

5 Discussion

Mathematical models have played an important role in the decision-making process in the control of FMD epidemics and its economic consequences (Garner and Lack, 1995; Ferguson et al., 2001; Keeling et al., 2001; Morris et al., 2001; Brentsen et al., 1992; Sanson and Morris et al., 1994; Nielen et al., 1996; Jalvingh et al., 1999; Bates et al., 2003). During the 2001 FMD epidemic in Great Britain, different approaches were used including "moment closure" techniques (Ferguson et al., 2001) and stochastic models (Keeling et al., 2001; Morris et al., 2001). Here, we used a spatially explicit deterministic model that takes into account the distance between counties in the transmission process (Figure 2), farm density within counties (Table 1), and information on the timing of intervention strategies during the epidemic. Our model was calibrated using data from the 2001 FMD epidemic in Uruguay and used to assess retrospectively the effects of the implementation of a mass vaccination programme while the epidemic was in progress. The model was not validated for predictive purposes. The goal here was to determine

whether or not the use of spatially explicit information as a proxy for animal rellocation and socio-economic individual movement (i.e., milk routes, human traffic) was enough to capture retrospectively the observed patterns of FMD spread. Notwithstanding the crude modelling assumptions made here, the spatially explicit model was able to capture regional patterns of the 2001 Uruguayan FMD epidemic, a feat that was not possible with a spatially homogeneous model.

Because observational epidemiology is a discipline that does not facilitate the implementation of controlled experimental designs, model evaluation is constrained to use simulated scenarios. Data obtained from the 2001 Uruguayan FMD epidemic were retrospectively used to assess the spatial model here described. However, case reporting of actual epidemics is likely to include errors not limited to delayed reporting and under-reporting. Therefore, this study should not be construed as an assessment of the epidemic that took place in Uruguay in 2001, but as a model evaluation that uses hypothetical geo-referenced and temporal epidemic data (although a very realistic dataset). That is, this model should be considered within the frame of the data here reported.

In spite of the fact that the spatial scenario chosen to compare the non-spatial (homogeneous mixing-based theory) and the spatial models was a region that most closely would resemble a homogeneous mix of susceptible farms (because it was where the epidemic began and where the highest proportion of cases was reported throughout the epidemic), significant differences were noticed between models. That supports the view that even in the most homogeneous

scenario, spatial differences occur, which make non-spatial models unlikely to capture the local complexities of epidemic processes. Mathematically, this can be expressed as differences due to non-random/non-uniform data distributions which is equal to say that spatial autocorrelation (disease clusters) were present (Moran, 1950).

Spread in our spatially explicit model is the result of two forces: a strong local internal force of infection linked to the global community via a weak long-distance force of infections. The fact that the force of infection fades with distance ultimately suggest that epidemics can only be supported if the light "fires" ignited by long distance dispersal are re-ignited by strong local contact dynamics. Under this scenario, the local reproductive number for spatial models must be very high for epidemics to occur (Holmes, 1997). Hence, it is not surprising to see high estimates for the values of the internal (within a county) reproductive numbers. The lower estimates for the reproductive number across counties (*external*) following movement restrictions show that, once movement restrictions had been put in place, the transmission process was mostly driven by within-county spread. That is, long-distance (at the level of counties) transmission became a rare event. These results are congruent with the rolling over of the intrinsic growth rate r (Figure 4a) and the parameter estimate $1/q = 0.97$ (km) which characterizes the average transmission range of the disease under the assumption of non-spatial heterogeneity.

The spatial epidemic model captured the observed two-peak outbreak in the transmission dynamics (Figure 6b). The two peak dynamics arise from long distance sparks of infection, which can trigger secondary outbreaks (Keeling et al., 2001). Secondary "peaks" of infection

can be of higher intensity, as can be observed from the epidemic (Figure 6b).

Further differences were noticed between models, when the daily number of infected farms was considered. A double epidemic peak was indicated by the spatial model, which seemed to contradict the expectation for epidemic decline after epidemic day 10th (shown in Fig 2), and the rapid decrease of Rinternal (Fig X). Because nation-wide vaccination was implemented since or after epidemic day 17th (European Commission DG (SANCO) report 3342/2001), it is not unconceivable that the movement of vaccinators and vehicles across farms could have become a vector for epidemic dispersal between infected (but not clinical) cases and susceptible animals, which could result in a second, although brief, epidemic peak.

Because of the good-fit observed between the spatial model and observed data, which differed significantly with that of the non-spatial model, it is concluded that even in scenarios where conditions might most closely resemble those of homogeneous mixing, spatial models are still more appropriate. Local spatial discontinuities may significantly differ from the assumptions required by homogeneous mixing models.

The epidemic data (2001 FMD epidemic in Uruguay) suffered from low reporting rates on weekends. In order to smooth out data inconsistencies, the parameter estimation procedure used was based on the cumulative epidemic curve. The error structure reflects the greater variability observed in the middle course of the epidemic and the lower variability observed at the beginning and towards the end of the epidemic, that is, the assumption that errors in the

data were independent was not made.

The lack of farm-level data, the spatial location of counties was used instead as a first order approximation in modelling the transmission dynamics of FMD resulted in the overestimation of internal reproductive numbers. The level of local and long-distance farm "interactions" naturally depend on farm "type." Data on farm heterogeneity (dairy, beef, etc) or farm composition (cattle, pigs, sheep) (Bates et al., 2001; Sutmoller et al., 2003) were not explicitly incorporated here but could be considered should appropriate data were to become available. Generally speaking, the estimates of the transmission rates (as previously defined) should be interpreted as mean transmission rates characteristic of the 2001 FMD epidemic in Uruguay. The explicit nature of the data and model assumptions suggest that these estimates are unlikely to be of value elsewhere. However, the modelling and estimation approach should be of use in similar situations.

The possibility of underreporting was not incorporated either. Underreporting comes from many sources such as from the farmer's not reporting clinically ill cases or from the fact that some animals, although infected, do not show clinical symptoms ("silent cases"). Once again, model results can easily overestimate the impact of interventions.

As in most models for FMD, our model does not include *road density* considerations but it could if such data were to become available. Road density could play a significant role in capturing higher resolution epidemic patterns within states or counties, a factor that is with

a great degree of county heterogeneity. During the epidemic in Uruguay, human traffic was not interrupted. Milk trucks continued to visit dairy farms and collect milk throughout the epidemic. The role played by these factors cannot be diminished.

There is little data on vaccine and quality or effectiveness of vaccination programme. Limitations include but are not limited to vaccination coverage (not all the susceptible animals are vaccinated for several reasons) and field vaccine efficacy. In the case of Uruguay, it is known that young calves (< 3 month-olds) were not vaccinated during the epidemic. Pigs and sheep were not vaccinated either (Reports of the European Commission). Furthermore, the vaccine used was specific to the virus observed during the FMD epidemic (virus type A_{24} (reports of the European Commission)) but no spatial/temporal data were available regarding whether or not vaccinal antibodies reached protective titers. In addition, age, health, and stress of the livestock influence an animal's response to and the effectiveness of the vaccine (the "responders" index) and some animals who exhibit an immune response do not reach protective antibody levels. In other words, plenty of data were not available and consequently, the model had to be developed using available data. It is again surprising to see that the use of space as a proxy for various sociological and epidemiological factors was enough to capture critical differences in dynamic patterns of spread.

It is suggested that models spatially explicit are particularly appropriate when interventions are planned or evaluated. Factors usually not accounted by non-spatial models (especially those involving vaccinations) include: a) vaccination efficacy, b) intervention spatial coverage, and c) percentage of animals and time required to synthesize specific antibody titers with protec-

tive levels (Fig Y). Vaccine efficacy is influenced by several factors (i.e., homology, safety and potency testing) (Sevilla et al., 1996, van Boven et al., 2000; Leforban, 1999; Garland, 1999). Vaccination programs require not only to achieve certain percentage of vaccinated animals (coverage) but also that that level be evenly achieved, since pockets of unvaccinated animals within vaccinated farms may allow the virus to re-invade (Keeling, 1999). Yet, we have failed to find literature reporting data on the spatial distribution of vaccination coverage. Antibody titer decay refers to post-vaccination animal immune response, which decreases 7% or more after 4-6 weeks post-vaccination (Armstrong and Mathew, 2001; Woolhouse et al., 1996). Antibody titer decay is also influenced by the age of the host. Age plays a minor effect in disease control of animals of relatively short life expectancy (thereby facilitating the success of vaccination as a disease control measure, as in foxes rabies), but a major role in control of diseases of animals of greater mean age, such as cattle (Woolhouse et al., 1997). Therefore, the intervention outcome may be influenced by multiple factors that are distributed over space in a non-random/non-uniform fashion.

It is concluded that major differences in outcomes may be expected when spatially explicit data are not considered. Absence of such data might explain the poor fit shown by the non-spatial model. In order to achieve greater precision, it is recommended the use of spatial data at the lowest possible scale (i.e., farm-level data, as opposed to county-level data).

6 Conclusions

- FMD epidemic models incorporating spatial structures can capture regional patterns of spread.

- Long-distance sparks of infection reaching areas of susceptible farms can generate multiple peaks in the global infection rates. In contrast to spatially structured models, spatially homogeneous models are unable to reproduce such patterns of infection.

- There was a rapid drop in the external reproductive number to less than one after movement restrictions were enforced. Following these restrictions, transmissions were localized and there was a very low probability for long-range transmission events. Hence, ensuring that movement restrictions are strictly enforced is crucial in any contingency plan against FMD.

- Given our model assumptions, mass vaccination implemented along with a policy of movement restrictions is an effective means of control and significantly reduces the final epidemic size.

- The 2001 FMD Uruguayan epidemic data and analysis can be used for comparison when assessing other control measures, such as culling policies and higher potency vaccines, implemented alone or in combination with other interventions.

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Tables & Figures

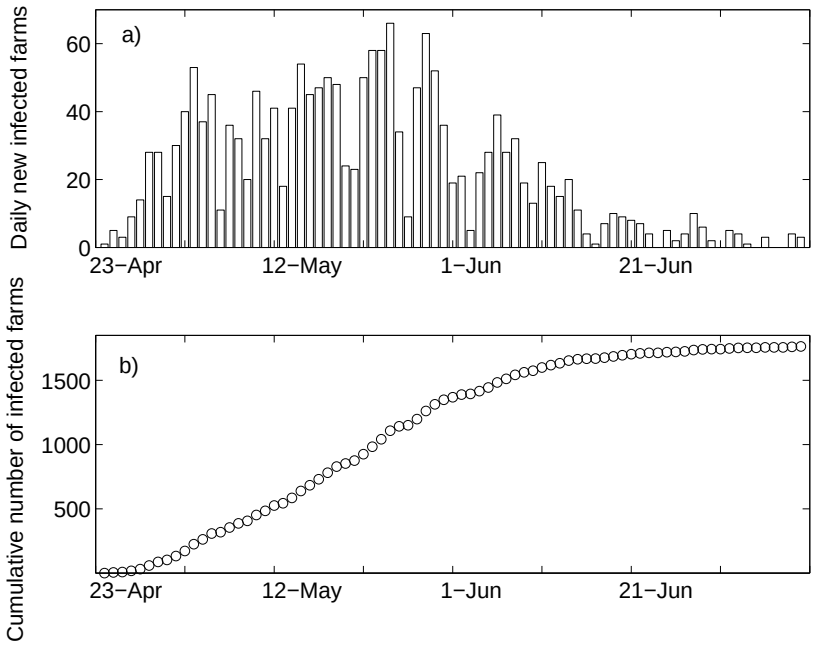

Figure 1: (a) Daily and (b) cumulative number of reported infected farms during the 2001 Foot and Mouth Disease epidemic in Uruguay. The epidemic reached its maximum of 66 outbreaks on day 33 (25 May 2001). By day 79 (10 July 2001) 1762 outbreaks had been reported. Data have been obtained from public records of the Uruguayan Ministry of Livestock, Agriculture, and Fisheries (MGAP), the Pan-american Health Organization, and the World Organization for Animal Health (OIE). The periodic dips in the data are due to low reporting rates on the weekends.

Table 1: Distribution of farm density and outbreaks of the 2001 foot-and-mouth disease epidemic in Uruguay over 79 epidemic days.

Region I					Region II					Region III				
State	Counties	N_j	Inf.	Tot.	State	Counties	N_j	Inf.	Tot.	State	Counties	N_j	Inf.	Tot.
Soriano	12	140	463	1682	Paysandu	13	121	64	1567	Artigas	12	118	34	1421
Colonia	18	151	362	2724	Salto	16	111	56	1783	Rivera	10	206	14	2064
Rio Negro	12	77	178	925	S. Jose	10	243	68	2430	C. Largo	16	196	26	2744
					Flores	9	91	62	816	Lavalleja	14	235	15	3296
					Florida	16	152	109	2436	Rocha	12	190	12	2284
					Tacuarembo	16	152	111	2427	T. y Tres	11	163	59	1797
					Durazno	15	136	92	2043	Maldonado	13	136	12	1773
										Canelones	23	141	25	3800

Counties, number of counties per state; N_j, mean number of farms per county; Inf., number of outbreaks per state; Tot., total number of farms per state.

Table 2: Parameter definitions and estimates obtained from least-squares fitting of nonspatial epidemic model (10) to the cumulative number of infected farms over time (days) in Region I (Figure 5a). All the parameters have units 1/ days.

Params.	Definition	Estim.	SD
$\hat{\beta}_0$	Average transmission rate between farms *before* mov. restrictions	0.77	0.04
$\hat{\beta}$	Average transmission rate between farms *after* mov. restrictions	0.49	0.08
$\hat{\alpha_0}$	Rate of detection of infected farms *before* mov. restrictions	0.16	0.07
$\hat{\alpha}$	Rate of detection of infected farms *after* mov. restrictions	0.14	0.02
$\hat{k}$	Rate of progression from latent to infectious state	0.26	0.07
$\hat{\nu}$	Vaccination rate of susceptible farms	0.16	0.04
$\hat{\mu}$	Rate at which vaccinated farms achieve protective levels	0.31	0.05

Table 3: Parameter definitions and estimates obtained from least-squares fitting of spatial epidemic model (3) to the cumulative number of infected farms over time (days) in Region I. All the parameters have units 1/ days except for q whose units are 1/Km. * Small values of q lead to widespread influence, while large values support local spread. Great mobility and frequent interactions among farms would lead to small values of q.

Params.	Definition	Estim.	SD
β_0	Average transmission rate within counties *before* mov. restrictions	0.33	0.13
β	Average transmission rate within counties *after* mov. restrictions	0.10	0.03
α_0	Rate of detection of infected farms *before* mov. restrictions	0.14	0.02
α	Rate of detection of infected farms *after* mov. restrictions	0.14	0.02
k	Rate of progression from latent to infectious state	0.28	0.05
q^*	Positive constant quantifying the extent of local spread	1.03	0.10
ν	Vaccination rate of susceptible farms	0.25	0.09
μ	Rate at which vaccinated farms achieve protective levels	0.14	0.03

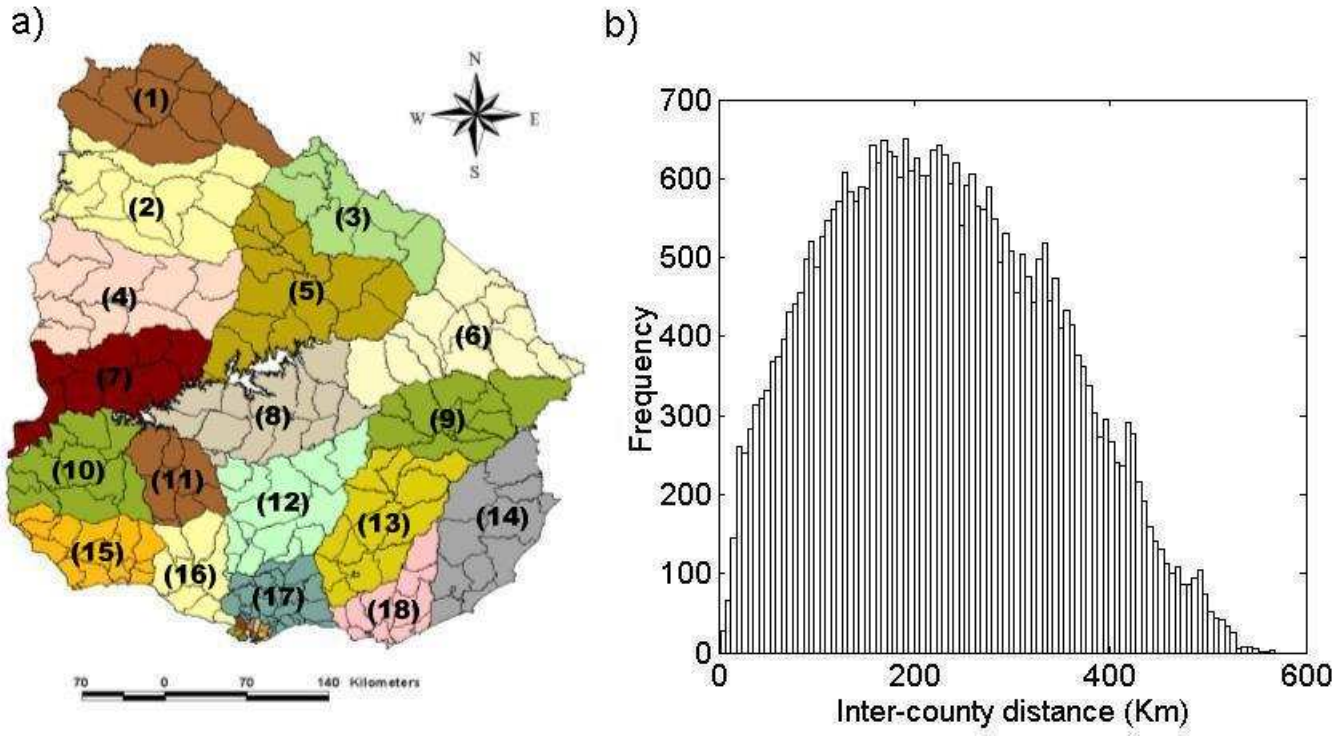

Figure 2: (a) Map of Uruguay with department (in color: 1) Artigas, 2) Salto, 3) Rivera, 4) Paysandu, 5) Tacuarembo, 6) Cerro Largo, 7) Rio Negro, 8) Durazno, 9) Treinta y Tres, 10) Soriano, 11) Flores, 12) Florida, 13) Lavalleja, 14) Rocha, 15) Colonia, 16) San Jose, 17) Canelones, 18) Maldonado) and county divisions and (b) distribution of intercounty (Euclidean) distances which were obtained using a geographic information system (GIS). The centroide of each county was used to compute euclidean distances.

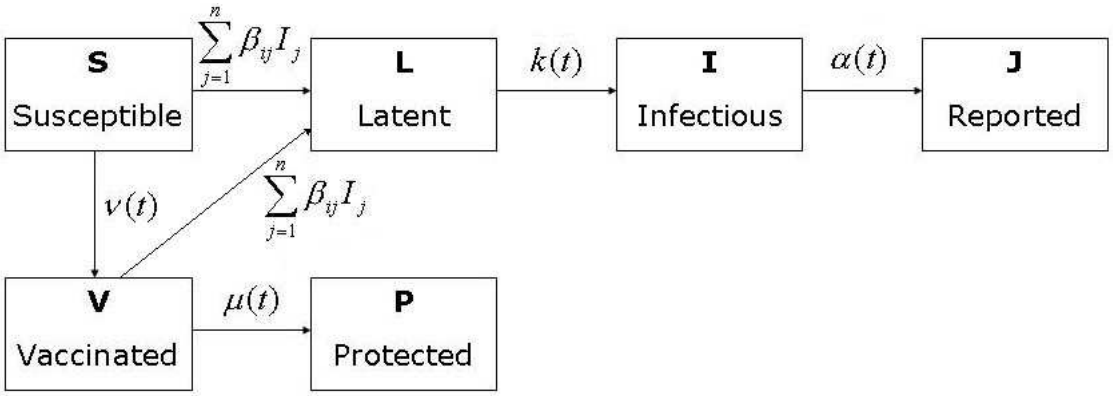

Figure 3: Schematic representation of the state progression for farms in a given county used to model the epidemic, as explained in the text.

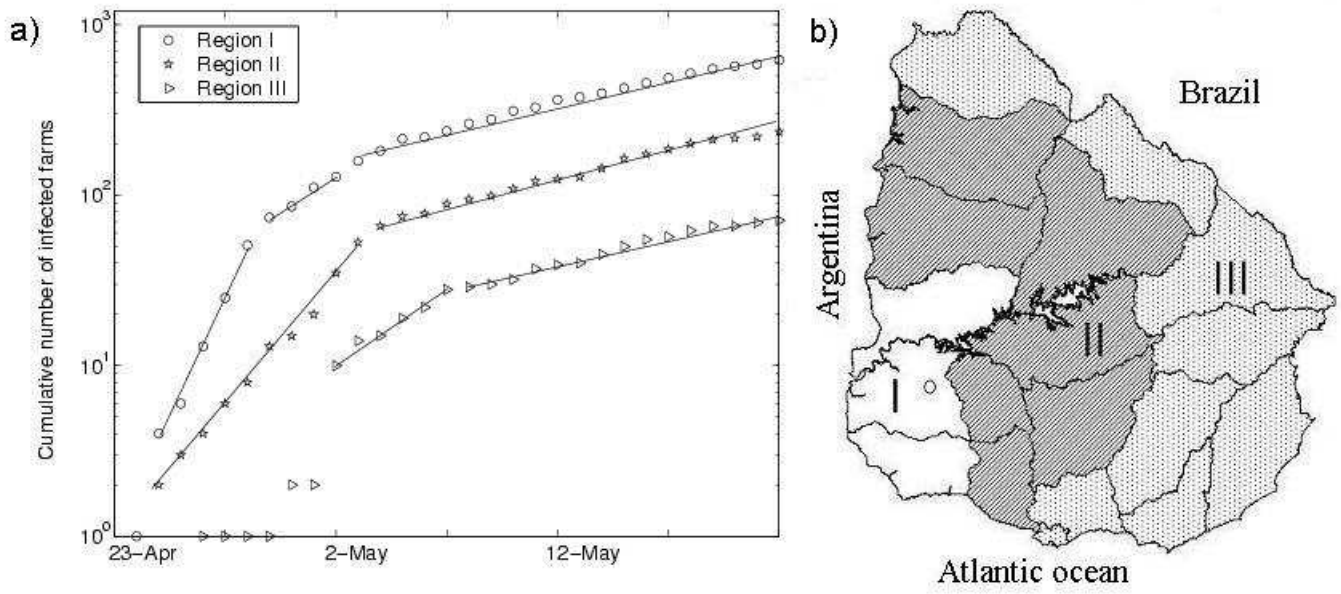

Figure 4: (a) The initial intrinsic growth rate r for Region I, II and III for the epidemic over 79 epidemic days. (b) Region I, II and III comprise 3, 7 and 8 Uruguayan states, respectively (see Table 1). The circle (Region I) denotes the site where the index case was reported.

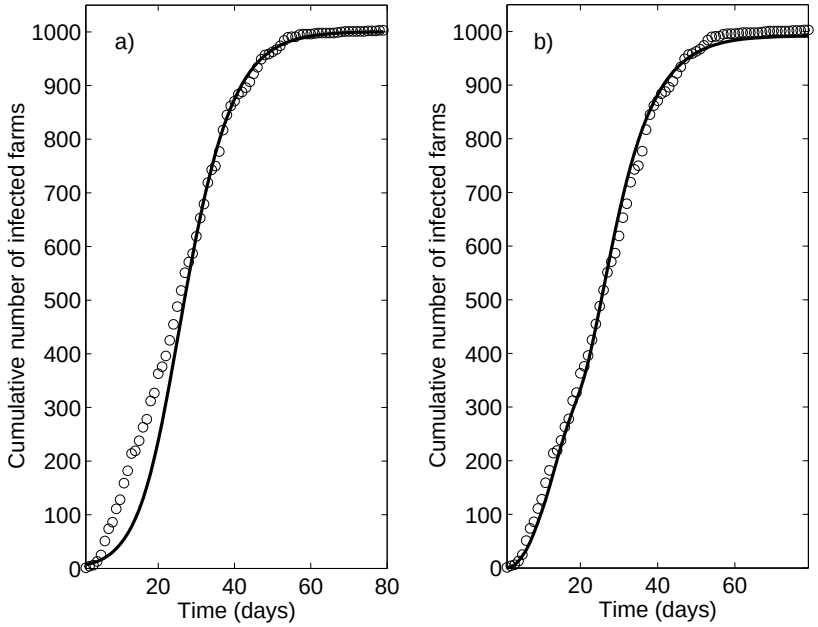

Figure 5: The cumulative number of reported infected farms in Region I (Figure 4), where the epidemic started (23 April 2001) and most outbreaks occurred. Circles are the data, and the solid line is the best-fit solution of (a) non-spatial model (10) and (b) spatial model (3) to the data by least-squares fitting, as explained in the text.

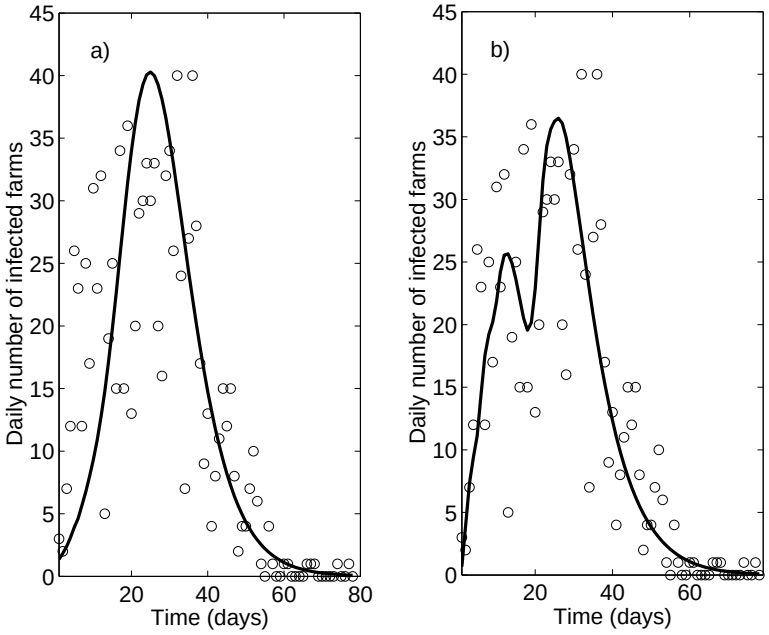

Figure 6: The daily number of reported infected farms in Region I (Figure 4), where the epidemic started (23 April 2001) and most outbreaks occurred. Circles are the data, and the solid line is the best-fit solution of (a) nonspatial model (10) and (b) spatial model (3) to the data by least-squares fitting, as explained in the text.

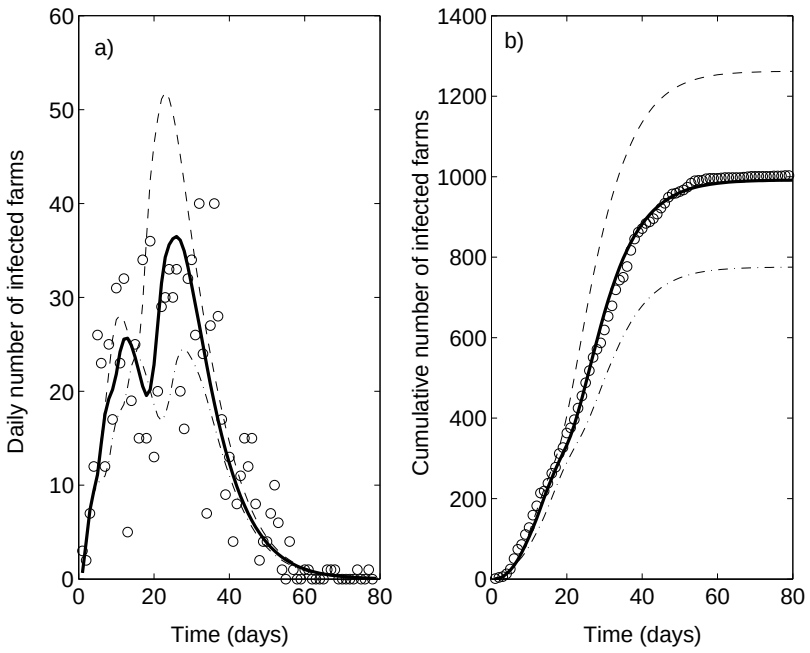

Figure 7: (a) The daily and (b) cumulative number of reported infected farms in Region I (Figure 4), where the outbreak started (23 April 2001) and most outbreaks occurred. Circles are the data, and the solid line is the best-fit solution of deterministic model equations (3) to the data by least-squares fitting (parameter estimates are given in Table 3). Two scenarios are shown: (dash-dash) movement restrictions with a 3-day delay and (dash-dot) 3 days before the actual date on which movement restrictions started.